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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	21

DATE MAILED: 07/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/585,817	SCHENK, DALE B.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,14-16,19 and 21-25* is/are pending in the application.

4a) Of the above claim(s) *1-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 14-16 19 21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 June 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *18* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

1. The Amendments filed 15 May 2003 (Paper No. 17) and 4 June 2003 (Paper No. 20) have been entered in full. Claims 11, 15, 16, and 21-25 have been amended. Claims 12, 13, 17, 18, 20, and 26-57 have been cancelled. Claims 1-10 remain withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected material, there being no allowable generic or linking claim. Claims 11, 14-16, 19, 21-25 are under examination.

2. The Applicant's continued traversal of the Restriction requirement as set forth in Office Action Paper No. 4 (21 September 2001) is noted and maintained for the reasons as set forth in Office Action Paper No. 15 (4 December 2002). The Examiner *accepts* "AScr" as a species of the "PrP" genus and thus both will be examined in the instant application.

3. The replacement copies for Citations #98, #250, and #278 have been received. Citation #98 has been taken into consideration. However, Citations #250 and #278 fail to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because they are not in the English language. They have been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

4. The Applicant has requested that the double patenting rejections be held in abeyance until indication of allowability in the instant application. The Examiner *accepts* this and herein

indicates whether or not the rejections under double patenting as set forth at pp. 11-14 ¶24-33 in the previous Office Action (Paper No. 15, 4 December 2002) have been *obviated* by amendment and if not, has maintained them where appropriate.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

6. The objection to the specification as set forth at pp. 4-5 ¶8-9 of the previous Office Action (Paper No. 15, 4 December 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 20, 4 June 2003).

7. The objection to the drawings as set forth at pp. 5 ¶10 of the previous Office Action (Paper No. 15, 4 December 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 20, 4 June 2003).

8. The objection to the claims as set forth at pp. 5 ¶11 of the previous Office Action (Paper No. 15, 4 December 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 20, 4 June 2003).

9. The rejection of claims 11-25 under 35 U.S.C. §101 (double patenting) as set forth at pp. 11 ¶24-25 of the previous Office Action (Paper No. 15, 4 December 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 20, 4 June 2003).

10. The rejection of claims 11-25 under 35 U.S.C. §112 ¶1 as set forth at pp. 11 ¶24-25 of the previous Office Action (Paper No. 15, 4 December 2002) is *withdrawn in part* in view of Applicant's amendments (Paper No. 20, 4 June 2003).

Maintained Objections And/Or Rejections

11. Claims **11, 14-16, 19,** and **21-25** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a method of treating a prion disorder in a mammalian subject, comprising administering to the subject a dosage of an amyloid component derived from a prion precursor protein (PrP) including genetic variants of the PrP associated with hereditary amyloidosis effective to produce an immune response comprising antibodies against said amyloid component and an adjuvant that augments the immune response to said amyloid component*, does not reasonably provide enablement for *prevention of a prion disorder in a mammalian subject using said method or use of other agents*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for the reasons as set forth in at pp. 5-11 ¶12-23 of the previous Office Action (Paper No. 15, 4 December 2002).

12. The Applicant traverses the 35 U.S.C. §112 ¶1 rejection of claims **11, 14-16, 19,** and **21-25** as set forth in at pp. 5-11 ¶12-23 of the previous Office Action (Paper No. 15, 4 December 2002) on the following grounds: **(a)** the PDAPP mouse model is a good mouse model for Alzheimer's disease, **(b)** post-filing publications provide evidence for the claimed method, **(c)** adequate guidance is presented to practice the invention, **(d)** it is not necessary to fully understand all the cellular and humoral effects of PrP to practice in the invention, **(e)** citing *In re Brana* (Fed. Cir. 1995) the Applicant argues that the USPTO is not responsible for testing therapies, **(f)** the mutations claimed are known in the art, **(g)** Tanaka's study was done without adjuvant, **(h)** the Smith and Weissman reference does not include use of an adjuvant, **(i)** a nexus

between active and passive immunization is present for prion diseases. Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons.

13. The instant claims are drawn very broadly to a method of treating prion disease via active immunization with PrP or an active immunogenic fragment of PrP known as "AScr" which is synonymous with PrP^{Sc} (pp. 20 of the Specification). The language of said claims encompasses both *treatment* and *prevention* prion disorders which covers a broad range of disorders.

14. The specification teaches that the administration of particular $A\beta_{42}$ (AN1792) fragments with an immunogenic adjuvant reduces β-amyloid levels within the brains of transgenic PDAPP mice. These mice exhibit Alzheimer type over production and build up of β-amyloid within the brain [Chapman (21/28 December 2000) "Model Behavior." Nature **408**: 915-916]. However, administration of $A\beta_{42}$ to Alzheimer's patients is not predictive of how administration of PrP affects patients with prion-related diseases or any given amyloid dependent disorders. There are no examples directed to PrP, diseases caused by PrP, or art-accepted PrP animal models.

15. Since the specification fails to provide any guidance for the successful prevention of prion disorders via active immunization, and since resolution of the various complications in regards to treating prion diseases and disorders is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations with known prion proteins, prion disorder signs and symptoms to correlate with prevention of said prion disorder. In the absence

of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

16. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed method of using PrP or AScr for active immunization in a patient to prevent a prion disorder. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a possibly toxic protein based solely on the performance of a different protein is highly problematic [see Weissman & Aguzzi (1997) "Bovine Spongiform encephalopathy and early onset variant Creutzfeldt-Jakob disease." Current Opinion in Neurobiology **7**: 695-700]. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed method for prevention, such a disclosure would not be considered enabling since the state of prion disorders is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

17. On "**(a)**", the Examiner *accepts* the Applicant's argument. The PDAPP mouse is a representative mouse model of Alzheimer's disease [see Chapman (21/28 December 2000) "Model Behavior." Nature **408**: 915-916]. However, the instant claims, as amended, are directed to prion diseases of which the PDAPP mouse is not an adequate model {see Goldfarb & Brown (1995) "The Transmissible Spongiform Encephalopathies." Annu. Rev. Med. **46**: 57-65 and

Aguzzi & Weissman (23 October 1997) "Prion research: the next frontiers." Nature **398**: 795-798}.

18. In response to "**(b)**", the Examiner *accepts* the Applicant's argument that the two references included and herein made of note [Sigurdsson *et al.* (July 2002) "Immunization Delays the Onset of Prion Disease in Mice." American Journal of Pathology **161**(1): 13-17 and Sigurdsson *et al.* (2003) "Anti-prion antibodies for prophylaxis following prion exposure in mice." Neuroscience Letters **336**: 185-187] offer support for use of active and passive immunization as a means of treatment for prion disease however, neither study shows prevention of prion diseases. In light of the breadth of the claims, "Prevention" is understood in the art to mean a total protection from disease or injury. Thus, given the high level of required effect, a high level of evidence showing prevention is also required. In fact, Sigurdsson et al. (July 2002) teaches:

> "Although neither of our treatment paradigms prevented prion disease, the close correlation between antibody levels and incubation time shows the promise of vaccination therapy for this untreatable and fatal neurodegenerative disease. Overall, the vaccination-mediated delay in the onset of prion disease is highly reproducible, correlates well with antibody titer, with the best therapeutic effect being obtained in mice preimmunized before infection." (pp. 15)

While the specification demonstrates a level of relief from symptoms using Aβ as an immunogen in mice and Applicant has provided compelling evidence to support the claimed method as a therapeutic method, total prevention was not achieved.

19. Concerning "**(c)**", the Examiner *accepts* the Applicant's argument in light of the post-filing references provided above.

20. Concerning "**(d)**", the Examiner *accepts* the Applicant's argument in light of the post-filing references provided above.

21. To address "**(e)**", the Examiner *accepts* the Applicant's argument that the USPTO is not responsible for testing the effectiveness of PrP or AScr immunizations. However, as Sigurdsson *et al.* (2003) teaches:

> "Although indicating the promise of immunologically-based therapy for prion disease, these prior studies were not designated to demonstrate the clinical relevance of prion-related immunization paradigms. It is also well known that PrP^{Sc} content does not necessarily correlate with disease progression." (pp. 186)

Taken into consideration, the Examiner accepts that the post-filing references provide guidance for treatment but not prevention or assurance of success with human patients.

22. In response to "**(f)**", the Examiner *accepts* the Applicant's argument in light of the current amendments. Yet Kovács *et al.* (2002) "Mutations of the Prion Protein Gene: Phenotypic Spectrum." J. Neurol. **249**: 1567-1582 teaches that 5-15% of prion disease are inherited and the age of onset, transmissibility, and severity of symptoms varies depends on the particular mutation of PrP (Table 1 & 2; Figure 4 and 5). Thus the skilled artisan is not presented with sufficient guidance in the instant Specification to practice the invention to the full scope of prevention of all the hereditary prion diseases {see also US 5750361 and Diomede *et al.* (1996) "Activation effects of a prion protein fragment [PrP-(106-126)] on human leucocytes." Biochem. J. **320**: 563-570}.

23. The issue in "**(g)**" is *moot* in view of Applicant's current amendment of claim 11.

24. The issue in "**(h)**" is *moot* in view of Applicant's current amendment of claim 11.

25. The argument presented in "**(i)**" is *withdrawn in part* in view of Sigurdsson *et al.* (July 2002) "Immunization Delays the Onset of Prion Disease in Mice." American Journal of Pathology **161**(1): 13-17 and Sigurdsson *et al.* (2003) "Anti-prion antibodies for prophylaxis following prion exposure in mice." Neuroscience Letters **336**: 185-187 as discussed above.

26. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of practicing the claimed method as a means of prevention when only treatment was demonstrated as exemplified in the references herein.

27. The rejection of claims **11, 14-16, 19,** and **21-25** under 35 U.S.C. §112 ¶1 is maintained.

28. The rejection of claims 11-25 under provisional obvious-type non-statutory double patenting as set forth at pp. 12-14 ¶26-33 in the previous Office Action (Paper No. 15, 4 December 2002) is *maintained.*

New Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

29. Claims **11, 14, 15,** and **16** are rejected under 35 U.S.C. 102(b) as being anticipated by Prusiner *et al.* (November 1993) "Ablation of the prion protein (PrP) in mice prevents scrapie and facilitates production of anti-PrP antibodies." PNAS **90**: 10608-10612. Prusiner *et al.* teaches the immunization of Prn-$p^{0/0}$ mice with scrapie prion proteins dispersed in Freund's

adjuvant to produce antibodies thus meeting the limitations of claims 11, 14, 15, and 16 (pp. 10611; Figure 3).

30. Claims **11, 14, 15,** and **16** are rejected under 35 U.S.C. 102(b) as being anticipated by WO 97/10505 (20 March 1997) Prusiner. WO 97/10505 teaches the production of antibodies via immunization of a host mammal (including but not limited to a mouse, rat, guinea pig, or hamster) with infectious PrP^{Sc} in mixture with an adjuvant such as incomplete Freund's adjuvant thus meeting the limitations of claims 11, 14, 15, and 16 (pp. 22-23, Example 2).

31. Claims **11, 14, 15,** and **16** are rejected under 35 U.S.C. 102(e) as being anticipated by US 2001/0021769 A1 (13 September 2001, filed 5 November 1996) Prusiner. US 2001/0021769 teaches the administration of PrP^{Scr} with complete Freund's adjuvant to produce antibodies in BALB/c mice thus meeting the limitations of claims 11, 14, 15, and 16 (paragraphs [0049-0050], [0089-0091]).

Summary

32. No claims are allowed.

33. The following articles, patents, and published patent applications were found by the Examiner during the prior art search and are here made of note:

a. US 5846533 (8 December 1998) Prusiner *et al.*

b. US 2002/0132268 A1 (19 September 2002) Chang & Lu

c. US 2002/0197258 A1 (26 December 2002) Ghanbari & Ghanbari

d. US 2002/0168377 A1 (14 November 2002) Schaetzl

e. Tal *et al.* (2003) "Complete Freund's Adjuvant Immunization Prolongs Survival in Experimental Prion Disease in Mice." Journal of Neuroscience Research **71**: 286-290

f. Wisniewski *et al.* (2002) "Therapeutics in Alzheimer's and Prion Diseases." Biochemical Society Transactions **30**(4): 574-578

34. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
July 11, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER